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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/554,945	CHEN ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *1,3-7 and 11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,8-10 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/22/00*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group II, Claims 2, 8-10, 12, in Paper No 6. is acknowledged and entered.

Claims 1-12 are pending in the instant application and Claims 1, 3-7, 11, have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Group II, Claims 2, 8-10, 12 are currently under prosecution.

OBJECTION

1. Claim 8 is objected to because claim 8 depends on non-elected claim 1.

2. Claim 2 is objected to, because claim 2(vi) contains a period (.) after thereof, which is within the claim.

3. Claim 2 is objected to because there are two 2(vi), and no 2(v). For the purpose of compact prosecution, it is assumed that the first 2(vi) is 2(v).

4. Claim 2 is objected to for the use of the language " a nucleotide sequence complementary to "said' isolated polynucleotide. It is not clear that said isolated polynucleotide is referred to which of the isolated polynucleotides of claim 2(i), (ii), (iii), (iv), (v) or (vi). For the purpose of compact prosecution, it is assumed that "said isolated polynucleotide is referred to any one of the isolated polynucleotides of 2(i), (ii), (iii), (iv), (v) or (vi).

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite because it is drawn to "stringent hybridization conditions". Stringent conditions are not defined by the claim (which reads on the full range of stringent conditions, that is from very permissive to very high stringency. The specification describes a single non-limiting example of stringent conditions (p.5, lines 12-19). Thus the specification does not provide a standard for ascertaining the requisite degree of stringent conditions and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention and would not be able to determine the metes and bounds of the claims.

REJECTION UNDER 35 USC 101, UTILITY

35 U.S.C. 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 2, 8-10, 12 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility.

Claims 2, 8-10, 12 are drawn to:

a) An isolated polynucleotide of SEQ ID NO:1 or an isolated polynucleotide encoding SEQ ID NO:2,

b) An isolated polynucleotide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:1, or a nucleotide sequence encoding SEQ ID NO:2, or an isolated polynucleotide encoding a polypeptide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2,

c) An isolated polynucleotide obtained by screening an appropriate library under stringent conditions with a labeled probe having the sequence of SEQ ID NO:1 or a fragment thereof,

d) a complement of said isolated polynucleotide (claim 1),

e) An expression system comprising a polynucleotide capable of producing the polypeptide of SEQ ID NO:2, or a polypeptide having at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2, a process for producing a recombinant host cell, and a recombinant host cell (claims 8-10), and

f) A process for producing a polypeptide comprising culturing the host cell of claim 10 (claim 12).

The specification discloses that the claimed nucleotide sequence of SEQ ID NO:1 shows homology with mouse secretogranin III (p.3, last paragraph), and is believed to be a member of the secretogranin III family, which may play an important role in signal transduction, and participates in secretory pathway (p.2, lines 11-15). The

disclosed utilities for the polynucleotide of SEQ ID NO: 1 or NPCABC08 include diagnosis, prevention and treatment of diseases associated with expression of SEQ ID NO:1, such as cancer, leukemia, diabetes mellitus, kidney disease, and autoimmune diseases, production of and screening of agonists, antibodies and antagonists that specifically bind to SEQ ID NO:2 encoded by the polynucleotide of SEQ ID NO:1 (specification, p.9-15).

However, neither the specification nor any art of record teaches what the claimed polynucleotide of SEQ ID NO:1 and the encoded polypeptide thereof are, what they do; they do not teach a utility for any of the variants claimed; they do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. The asserted utilities for SEQ ID NO:1, or the encoded polypeptide, such as production of and screening of agonists, antibodies and antagonists apply to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to SEQ ID NO:2 encoded by the claimed polynucleotide of SEQ ID NO:1. Additional disclosed utilities for SEQ ID NO:1 include therapy and diagnosis of conditions and diseases characterized by expression of SEQ ID NO:1. The asserted utility of SEQ ID NO:1 is based on the assertion that: 1) SEQ ID NO:2, encoded by SEQ ID NO:1 has chemical and structural homology to mouse secretogranin III (p.3, last paragraph). A sequence similarity search MPSRCH in commercial database reveals that SEQ ID NO:1 is 79% similar with a mouse secretogranin III from nucleotide 1 to nucleotide 1969 (Dopazo et al, 1993, Genbank Sequence Database (Accession U02983), National Center for Biotechnology

Information, National Library of Medicine, Bethesda, Maryland, or J Mol NeuroSci, 4(4): 225-233, and MPSRCH search report, 20023, us-09-554-945b-1.rge, pages 11-12).

It is noted that the specification does not disclose that SEQ ID NO:1 is differentially expressed in disease tissues as compared to normal tissues, such that SEQ ID NO:1 could be used for diagnosis of diseases.

It is clear that, although there is a 79% identity between secretogranin III and SEQ ID NO:1, there is a 21% dissimilarity between SEQ ID NO:1 and secretogranin III; and the effects of these dissimilarities upon protein structure and function cannot be predicted. Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instructions of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al (J of Cell Bio. 111:2129-2138, 1990) who teach that

replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein and by Lazar et al (Molecular and Cellular Biology, 1988, 8:1247-1252) who teach that in transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen. These references demonstrate that even a single amino acid substitution will often dramatically affect the biological activity and characteristics of a protein. Clearly, with 21% dissimilarity to secretogranin III, the function of the SEQ ID NO:1 could not be predicted, based on sequence similarity with secretogranin III, nor would it be expected to be the same as that of secretogranin III. In addition, Bork (Genome Research, 2000,10:398-400) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of the known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col 1). One of the reasons for the inaccuracy is that the quality of data in public sequence databases is still insufficient. This is particularly true for data on protein function. Protein function is context dependent, and both molecular and cellular aspects have to be considered (p. 398, col 2). Conclusions from the comparison analysis are often stretched with regard to protein products (p. 398, col 3). Furthermore, recent studies show that alternative splicing might affect more than 30% of human genes and the number of known post-

translational modifications of gene products is increasing constantly so that complexity at protein level is enormous. Each of these modifications may change the function of respective gene products drastically (p. 399, col 1). Further, although gene annotation via sequence database searches is already a routine job, even here the errror rate is considerable (p. 399, col 2). Most features predicted with an accuracy of greater than 70% are of structural nature and at best only indirectly imply a certain functionality (see legend for table 1, page 399). As more sequences are added and as errors accumulate and propagate it becomes more difficult to infer correct function from the many possibilities revealed by database search (p. 399para bridging cols 2 and 3). The reference finally cautions that although the current methods seem to capture important features and explain general trends, 30% of those feature are missing or predicted wrogngly. This has to be kept in mind when processing the results further (p. 400, para bridging cols 1 and 2). Further, Scott et al (Nature Genetics, 1999, 21:440-443) teach that the gene causing Pendred syndrome encodes a putative transmembrane protein designated pendrin. Based on sequence similarity data, the authors postulated that the putative protein was deemed to be a member of sulfate transport proteins that included a 29% identity to rat sulfate-anion transporter, 32% similarity to human diastrophic dysplasia sulfate transporter, and 45% similarity to the human sulfate transporter "downregulated in adenoma". However, upon analyzing the expression and kinetics of the protein, the data revealed no evidence of sulfate transport wherein results revealed that pendrin functioned as a transporter of chloride and iodide. Scott et al. suggest that these results underscore the importance of confirming the function of newly identified

gene products even when the database searches reveal significant homology to proteins of known function (page 411, 1st column, 4th paragraph).

Clearly, given not only the teachings of Bowie et al, Lazar et al, Burgess et al and Scott et al, but also the limitations and pitfalls of using computational sequence analysis and the unknown effects of alternative splicing, post translational modification and cellular context on protein function as taught by Bork, with a 21% dissimilarity to a mouse secretogranin III, the function of the SEQ ID NO:1 could not be predicted, based on sequence similarity with a mouse secretogranin III, nor would it be expected to be the same as that of the mouse secretogranin III.

Further, even if SEQ ID NO:1 encodes a mouse secretogranin III -like protein, neither the specification nor any art of record teaches what the polypeptide is, what it does. The specification does not teach a relationship to any specific disease or establish any involvement of the polynucleotide and the encoded polypeptide thereof in the etiology of any specific disease.

In the absence of any disclosed relationship between the claimed polynucleotide and the encoded polypeptide thereof and any disease or disorder and the lack of any correlation between the claimed polynucleotide and the encoded polypeptide thereof with any known disease or disorder, and further in view that any potential diagnostic or therapeutic utility is not yet known and has not yet been disclosed, the utility is not substantial. Further research is necessary to determine what use is for the claimed polynucleotide or the encoded polypeptide thereof. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as

an object of use-testing." *Brenner*, 148 USPO at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

For reasons set forth above the disclosure satisfies none of the three criteria of a specific, substantial, and credible utility. *See In re Kirk*, 153 USPO 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polynucleotides. Because the claimed invention is not supported by a specific, substantial asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 2, 8-10, 12 are rejected under 35 U.S.C. 112, first paragraph.

Specifically, since the claimed invention is not supported by specific, substantial utility or a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The following is a quotation of the first paragraph of 35 USC 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

. Claims 2, 8-10, 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 2, 8-10, 12 are drawn to:

a) An isolated polynucleotide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:1, or a nucleotide sequence encoding SEQ ID NO:2, or an isolated polynucleotide encoding a polypeptide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2 (claim 2),

b) An isolated polynucleotide obtained by screening an appropriate library under stringent conditions with a labeled probe having the sequence of SEQ ID NO:1 or a fragment thereof, or a complement of said isolated polynucleotide (claim 2),

c) An expression system comprising a polynucleotide capable of producing the polypeptide of SEQ ID NO:2, or a polypeptide having at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2, a process for producing a recombinant host cell, and a recombinant host cell (claims 8-10), and

d) A process for producing a polypeptide comprising culturing the host cell of claim 10 (claim 12).

The disclosure of the specification has been set forth above, under 101 rejection.

The specification further discloses that hybridization techniques are well known in the art and that the "preferred" stringent hybridization conditions "include" overnight incubation at 42 C, in 50% formamide, 5x SSC, 50 mM sodium phosphate, 5x Denhardt's solution, 10% dextran sulfate, and sheared salmon sperm DNA, followed by washing in 0.1XSSC at about 65 C (p.5, lines 12-19).

Based on the disclosure in the specification, one would reasonably interpret that stringent conditions would span from very low stringency to very high stringency, wherein under low stringent condition unrelated sequences would hybridize or attach to the claimed labeled probe.

Further, it is noted that an isolated polynucleotide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:1, or a nucleotide sequence encoding SEQ ID NO:2, or an isolated polynucleotide encoding a polypeptide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2 encompasses unrelated polynucleotide sequence with unknown structure, or a polynucleotide encoding unrelated polypeptide with unknown structure, provided they share 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:1 or SEQ ID NO:2, respectively.

It is also noted that an isolated polynucleotide obtained by screening an appropriate library under stringent conditions with a labeled probe having the sequence of SEQ ID NO:1 or a fragment thereof encompasses unrelated polynucleotide obtained from screening a library, by using as probe SEQ ID NO:1 or any fragment of SEQ ID

NO:1, which is not necessary specific for SEQ ID NO:1, under hybridization conditions which could be very low stringent conditions, because under very low hybridization condition, it is expected that unrelated sequences would hybridize to SEQ ID NO:1, and because using as a probe SEQ ID NO:1, or a fragment thereof, one would expect unrelated sequences sharing a fragment with SEQ ID NO:1 would hybridize to said probe, even under the most stringent hybridization conditions.

Moreover, a complement of the claimed isolated polynucleotide would encompass unrelated sequence, because a complement could be partial or full length complement, wherein a partial complement could share with the claimed isolated polynucleotide only a few complementary nucleotides.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*. (See page 1117). The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every

species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA..."requires a precise definition, such as by structure, formula, chemical name, or physical properties", not a mere wish or plan for obtaining the claimed chemical invention".

Support for variants is provided in the specification on page 3, second paragraph and p. 5, first paragraph, where it is disclosed that the invention encompasses variants having 70%, 80%, 90%, 95%, 97%, 98-99% identity with SEQ ID NO:1 or the encoded polypeptide of SEQ ID NO:2. However, no disclosure of the structure of the claimed variants is made in the specification. This is insufficient to support the generic claims as provided by the Written Description Guidelines.

The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polynucleotides.

The claims read on polynucleotide variants of SEQ ID NO:1, or nucleotide sequences encoding variants of SEQ ID NO:2 , wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the nucleic acid or peptide, as well as insertions and deletions, provided that the resulted variation is up to 5%-30% difference with SEQ ID NO: 1 or SEQ ID NO:2. The specification and the claims do not disclose any limit on which amino acid that is subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original

amino acids. Thus the scope of the claims includes numerous structural polynucleotide variants, and nucleotide sequences encoding numerous structural variants. The specification and the claims do not provide any guidance as to which, or how many original amino acid(s) that are naturally substituted, or to which type of substitution besides conservative substitution, or which amino acids that are naturally deleted or inserted so that the claimed polypeptide could function as contemplated. No common structural attributes that identify the claimed structural polynucleotide variants and nucleotide sequences encoding the polypeptide variants are disclosed. In addition, no common functional attributes that identify the claimed structural polynucleotide variants and nucleotide sequences encoding the polypeptide variants are disclosed, because the function of a nucleotide sequence could be abolished, even with substitution of only one amino acid of the peptide encoded by said nucleotide sequence (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138).

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of specific nucleotide sequences and the ability to screen, is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Therefore only an isolated DNA molecule comprising the polynucleotide sequence of SEQ ID NO:1, and polynucleotides encoding SEQ ID NO:2, but not the full

breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE OF ENABLEMENT

1. If Applicant could overcome the above 101 and 112, first paragraph rejection, claims 2, 8-10, 12 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO:1, **does not reasonably provide enablement for a polynucleotide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:1**, or a nucleotide sequence encoding SEQ ID NO:2, or an isolated polynucleotide **encoding a polypeptide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2, or an isolated polynucleotide obtained by screening under stringent conditions with a labeled probe having the sequence of SEQ ID NO:1, or fragment thereof, or a complement of said isolated polynucleotide .** The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 2, 8-10, 12 are drawn to:

a) An isolated polynucleotide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:1, or a nucleotide sequence encoding SEQ ID NO:2, or an isolated polynucleotide encoding a polypeptide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2 (claim 2),

b) An isolated polynucleotide obtained by screening an appropriate library under stringent conditions with a labeled probe having the sequence of SEQ ID NO:1 or a fragment thereof, or a complement thereof (claim 2),

c) An expression system comprising a polynucleotide capable of producing the polypeptide of SEQ ID NO:2, or a polypeptide having at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2, a process for producing a recombinant host cell, and a recombinant host cell (claims 8-10), and

d) A process for producing a polypeptide comprising culturing the host cell of claim 10 (claim 12).

Based on the disclosure in the specification, one would reasonably interpret that stringent conditions could span from very low stringency to very high stringency.

Further, it is noted that an isolated polynucleotide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:1, or a nucleotide sequence encoding SEQ ID NO:2, or an isolated polynucleotide encoding a polypeptide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2 encompasses a polynucleotide variant of SEQ ID NO:1 or a polynucleotide encoding a variant of the encoded polypeptide of SEQ ID NO:2, with unknown structure and function, provided they have a difference of at least 5%, 10%, 20% or 30 % with SEQ ID NO:1 or 2.

It is also noted that an isolated polynucleotide obtained by screening an appropriate library under stringent conditions with a labeled probe having the sequence of SEQ ID NO:1 or a fragment thereof, or a complement thereof encompasses unrelated polynucleotide obtained by using SEQ ID NO:1 or any fragment of SEQ ID NO:1, which is not necessary specific for SEQ ID NO:1, under hybridization conditions which could be very low stringent conditions.

Moreover, a complement of the claimed isolated polynucleotide would encompass unrelated sequence, because a complement could be partial or full length complement, wherein a partial complement could share with the claimed isolated polynucleotide only a few complementary nucleotides.

Applicant has not shown how to make and use the claimed variant polynucleotides, and nucleotide sequences encoding the polypeptide variants which are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Such unpredictability would equally apply to DNA sequences which encode proteins. For example, Bowie et al (Science, 1990, 257 : 1306-1310) teach that an amino acid sequence encodes a message that determine the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and carry out the instruction of the genome and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex (col.1, p.1306). Bowie et al further teach that while it is

known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitution can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col.2, p.1306). The sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Burgess et al, (Journal of Cell Biology, 1990, 11: 2129-2138), who teach that replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In addition, although conservative subsititution would not destroy the biological function of a protein, the specification fails to disclose which amino acid(s) are naturally subjected to conservative substitution. In the absence of a source of method of making such variants, one of skill in the art would be forced into undue experimentation to practice the claimed invention as broadly as claimed.

Further, the claim 2 encompass polynucleotides comprising non-disclosed nucleic acid sequences attached to or detected by a non-specific fragment of SEQ ID NO:1, or by SEQ ID NO:1. As conventionally understood in the art and as taught by US Patent No. 5,912,143, hybridization is used to refer to any process by which a strand of nucleic acid binds with a complementary strand through base pairing (col 5, lines 3-5) and further teaches that numerous equivalent conditions may be employed to comprise either low or high stringency conditions and hybridization solutions my be varied to generate conditions of either low or high stringency (col 5, lines 57-67). The "stringent hybridizing" as claimed read on both high and low stringency conditions. It is well known that the lower the stringency condition the more dissimilar the hybridizing molecule will be from the molecule to which it hybridizes. For example, Sambrook et al, eds, 1989, 2nd ed, Molecular Cloning, a laboratory manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, p. 11.52, teach that the temperature of hybridization, (which is related to the degree of stringency) should be high enough to suppress hybridization of the probe to incorrect sequences. Sambrook et al further teach that if the probe hybridizes indiscriminately, repeat the hybridization at a higher temperature or wash under conditions of higher stringency (p. 11.52, last two lines).

When given the broadest reasonable interpretation, the claims are clearly intended to encompass a variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the hybridizing molecules encompassed by the claims **would not** share either structural or functional properties with SEQ ID NO:1.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to use the claimed invention as broadly as claimed.

2. If Applicant could overcome the above 101 and 112, first paragraph rejection, claims 8-10, 12 are still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated host cell comprising a vector or an expressing system comprising SEQ ID NO:1, **does not reasonably provide enablement for " a host cell"** comprising a vector or an expressing system comprising SEQ ID NO:1, or variants thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 8-10, 12 are drawn to:

a) An expression system comprising a polynucleotide capable of producing the polypeptide of SEQ ID NO:2, or a polypeptide having at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2, wherein said expression sytem is present in a compatible host cell, a process for producing a recombinant host cell, and a recombinant host cell produced by said process (claims 8-10), and

e) A process for producing a polypeptide comprising culturing the host cell of claim 10 (claim 12).

The specification contemplates gene therapy, using retroviral expression construct containing RNA encoding the polypeptide of the claimed invention, for

engineering cells in vivo and expression of the polypeptide in vivo (p.14, first paragraph).

In view of the disclosure in the specification, the claims encompass an expression vector expressing the claimed sequence present in a compatible in vivo host cell, and an in vivo host cell expresssing the claimed sequence obtained from gene therapy.

There is however no teaching in the specification of how to successfully obtain an in vivo host cell expressing the claimed sequence.

On cannot extrapolate the teaching in the specification to the scope of the claim. The state of the gene therapy art at the time of filing was that the combination of vector, promoter, protein, cell, target tissue, level of expression and route of administration required to target the tissue of interest and obtain a therapeutic effect using gene therapy was unpredictable. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under

experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable,

the specification would need more detail as how to make and use the invention in order to be enabling."

In view of the unpredictability of gene therapy, the lack of any disclosure of how to successfully obtain in vivo host cells comprising or expressing the claimed polynucleotide, and the lack of objective evidence of obtaining in vivo host cells comprising or expressing the claimed polynucleotide, it would be undue experimentation for one of skill in the art to practice the claimed invention.

3. If Applicant could overcome the above 101 and 112, first paragraph rejection, claim 12 is still rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for producing a polypeptide encoded by SEQ ID NO:1, **does not reasonably provide enablement for a process for producing "a" polypeptide**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 12 is drawn to a process for producing "a" polypeptide comprising culturing the host cell produced by transforming or transfecting a cell with an expression system comprising a polynucleotide capable of producing the polypeptide of SEQ ID NO:2, or a polypeptide having at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2, wherein under appropriate culture conditions, said host cell produces a polypeptide having at least 70% identity to the entire length of SEQ ID NO:2.

Claim 12 encompasses a process for producing "any" polypeptide comprising culturing the host cell produced by transforming or transfecting a cell with an expression system comprising a polynucleotide capable of producing the polypeptide of SEQ ID NO:2, or a polypeptide having at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2, wherein under appropriate culture conditions, said host cell produces a polypeptide having at least 70% identity to the entire length of SEQ ID NO:2, and recovering the polypeptide from the culture.

One would not expect that the claimed polynucleotide sequence could produce unrelated polypeptides in a host cell, because said unrelated polypeptides would have different structure, and would not be expected to be translated from the claimed polynucleotide sequence.

The specification does not disclose how to translate the claimed polynucleotide sequence into any polypeptide having any structure.

Further, it is noted that a host cell could produce in the cell polypeptides with various levels of concentration, by normal process of translation of expressed RNA sequences, which are structurally different from SEQ ID NO:1.

The specification however does not disclose which polypeptide(s) different from the polypeptide encoded by SEQID NO:1 or variants thereof is intended to be recovered, nor how to recover any of these polypeptides, some of which could exist only under very low concentration. Nor does the specification disclose the

structure of the numerous polypeptides produced by the claimed method, such that one could make said claimed polypeptides.

In view of the above, and in the absence of the teaching in the specification of how to obtain any polypeptide from the cultured host cell, it would be undue experimentation for one of skill in the art to practice the claimed invention.

REJECTION UNDER 35 USC 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Dopazo et al, 1993, Genbank Sequence Database (Accession U02983), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, or J Mol NeuroSci, 4(4): 225-233, 1993.

Claim 2 is drawn to an isolated polynucleotide obtained by screening an appropriate library under stringent conditions with a labeled probe having the sequence of SEQ ID NO:1 or a fragment thereof.

It is noted that claim 2 is a product by process and thus is treated as a product per se, i.e. a polynucleotide that hybridizes under stringent conditions with a labeled probe having the sequence of SEQ ID NO:1 or a fragment thereof.

Further, it is noted that an unrelated polynucleotide could hybridizes via a common fragment to SEQ ID NO:1 or fragment thereof under the most stringent conditions. Moreover, there is no definition of stringent condition in the specification, and a stringent condition encompasses from very low stringent to very high stringent condition, wherein under very low stringent hybridization condition, one would expect unrelated sequences would hybridize to the probe having the sequence of SEQ ID NO:1.

Dopazo et al, 1993, teach a mouse secretogranin III polynucleotide sequence, which 79% similar to SEQ ID NO:1, from nucleotide 1 to nucleotide 1969, under MPSRCH sequence similarity search (MPSRCH search report, 2003, us-09-554-945b-1.rge, pages 11-12).

Given the 79% identity with SEQ ID NO:1, it would be expected that the sequence taught by Dopazo et al would hybridize under stringent conditions to SEQ ID NO:1, or a fragment thereof.

Thus the polynucleotide sequence taught by Dopazo et al seems to be the same as the claimed polynucleotide sequence.

2. Claim 2 is rejected under 35 USC 102(b) as being anticipated by Dopazo et al, 1993, J Mol NeuroSci, 4(4): 225-233, Genbank Sequence Database (Accession

number: U02983), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland.

Claim 2 is drawn to an isolated polynucleotide encoding a polypeptide that has at least 70%, or 80% identity to the entire length of SEQ ID NO:2.

Dopazo et al teach a mouse secretogranin III polypeptide sequence, which 87% similar to the entire length of the polypeptide of SEQ ID NO:2, from amino acid 1 to amino acid 468, under MPSRCH sequence similarity search (MPSRCH search report, 2003, us-09-554-945b-2.rsp, page 2). Said mouse secretogranin III polypeptide sequence is encoded by the mouse secretogranin III polynucleotide sequence, taught by Dopazo et al, which 79% similar to SEQ ID NO:1, from nucleotide 1 to nucleotide 1969, under MPSRCH sequence similarity search (MPSRCH search report, 2003, us-09-554-945b-1.rge, pages 11-12).

Thus the polynucleotide sequence taught by Dopazo et al seems to be the same as the claimed polynucleotide sequence.

3. Claim 2 is rejected under 35 USC 102(b) as being anticipated by Dopazo et al, 1993, Genbank Sequence Database (Accession U02983), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, or J Mol NeuroSci, 4(4): 225-233, or Boehringer Mannheim Biochemicals, 1994 Catalog, p. 93.

Claim 2 is drawn to a "complement" of :

a) An isolated polynucleotide of SEQ ID NO:1 or an isolated polynucleotide encoding SEQ ID NO:2,

b) An isolated polynucleotide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:1, or a nucleotide sequence encoding SEQ ID NO:2, or an isolated polynucleotide encoding a polypeptide that has at least 70%, 80%, 90% or 95% identity to the entire length of SEQ ID NO:2,

c) An isolated polynucleotide obtained by screening an appropriate library under stringent conditions with a labeled probe having the sequence of SEQ ID NO:1 or a fragment thereof

It is noted that a complement could be partial or full length complement, wherein a partial complement could share with the claimed isolated polynucleotide only a few complementary nucleotides.

Dopazo et al, 1993, teach a mouse secretogranin III sequence, which 79% similar to SEQ ID NO:1, from nucleotide 1 to nucleotide 1969, under MPSRCH sequence similarity search (MPSRCH search report, 2003, us-09-554-945b-1.rge, pages 11-12).

The Boehringer Mannheim teaches a kit comprising random primers that encompass all possible 6-nucleotide sequences (see page 93, Catalog No. 1034 731/1006 924).

Given the polynucleotide sequence taught by Dopazo et al, one of ordinary skill in the art would immediately envision the claimed complementary sequence.

Furthe, the random primers taught by Boehringer Mannheim seem to be the same as the claimed complementary sequence.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

PATENT EXAMINER

December 30, 2003